EXHIBIT A

Lasers in Cutaneous and Aesthetic Surgery

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for all photobiologic effects and laser-tissue interactions to occur. The

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injury occurs. The relatively low power continuous-wave lasers such as the CO_2 and argon-ion laser and the quasi–continuous-wave (rapid-pulsed) lasers such as the copper vapor and KTP lasers usually cause a well-controlled, superficial, partial-thickness burn. In contrast, pulsed yellow-dye lasers designed for selective photothermolysis of microvascular lesions selectively coagulate microvessels.

Selective photothermolysis is a term coined by Dr. Parrish and myself[10] over 14 years ago to describe the sequence of light-heat-ruin that occurs at microscopic sites, such as blood vessels, pigmented cells, and tattoo ink particles, which selectively absorb light pulses. Selective photothermolysis is qualitatively different from gross thermal injury and is like a "magic bullet" in its ability to target certain structures. Short pulses are necessary to deposit energy in the targets before they can cool off, thus achieving extreme, localized heating of the targets. Thermal coagulation or thermally mediated mechanical damage, or both, are involved, depending on the rate of energy deposition in the targets. This technique led to the development of a new generation of dermatologic lasers that cause much less scarring, and these are discussed in detail here.

Mechanical injury, sometimes misnamed "photoacoustic injury," occurs as the result of the rapid heating produced by high-energy, short-pulse lasers. The rate of local heating can be so severe that structures are torn apart by *shock waves* (a highly destructive supersonic pressure wave), *cavitation* (the sudden expansion and collapse of a steam bubble), or rapid *thermal expansion*. Terms such as *fracture, rupture,* or *explosion* are appropriately used in reference to these processes, even though they occur on a microscopic scale. Mechanical damage plays a central, positive role in the tattoo removal achieved by selective photothermolysis using high-energy, submicrosecond lasers. However, mechanical damage can also be an unwanted side effect, such as in the form of the bleeding caused by pulsed yellow-dye lasers and the ejection of tissue fragments caused by high-energy, Q-switched laser pulses.

Thermal Injury to Cells

Most human cells can withstand prolonged exposure to a temperature of 40°C. At 45°C, cultured human fibroblasts have been observed to be destroyed after about 20 minutes of exposure. However, the same cells can withstand a temperature of more than 100°C if exposed to it for only 10^{-3} seconds.[11] Thus, it is not the temperature per se but a combination of the local temperature and the heating time that determines whether cells in the skin are injured. This is presumably because thermal denaturation is a rate-dependent process, as described earlier. This behavior has an important bearing on the cell injury that occurs in the setting of selective photothermolysis, during which extreme temperatures are present in target sites, such as microvessels, for a very short duration. Essentially nothing is known

Light deposits energy only at sites of absorption. Heat is created at wavelengths that penetrate into skin and are preferentially absorbed by chromophoric structures, such as blood vessels or melanin-containing cells. As soon as the heat is created, however, it begins to dissipate as the result of conduction and radiative transfer. Thus, the competition between active heating and passive cooling determines how hot the targets become. The most selective target heating is achieved when the energy is deposited at faster than the rate of cooling of the target structures.

Three basic elements are necessary to achieve selective photothermolysis: (1) a wavelength that reaches and is preferentially absorbed by the desired target structures, (2) an exposure duration less than or equal to the time necessary for cooling of the target structures, and (3) sufficient fluence to produce a damaging temperature in the target structures. When these criteria are met, exquisitely selective injury occurs in thousands of microscopic targets, without the need to aim the laser at each one. The effect is equivalent to the legendary magic bullets that seek out only the desired target. Selective photothermolysis makes use of a variety of thermally mediated damage mechanisms, including thermal denaturation, mechanical damage resulting from rapid thermal expansion or phase changes (cavitation), and pyrolysis (changes in the primary chemical structure).

A useful construct is the *thermal relaxation time*, mentioned earlier. When the laser exposure duration is less than the thermal relaxation time, maximal thermal confinement occurs because the target cannot then get rid of its heat during the laser exposure. Many processes are involved in cooling, including convection, radiation, and conduction. Of these, thermal conduction is the one that dominates the cooling of microscopic structures in skin. However, microscale radiational cooling in tissue has never been thoroughly examined and in theory may be of importance for very small targets at high temperatures, such as tattoo ink particles or melanin granules.

It is common experience that smaller objects cool more quickly than larger objects. For example, a cup of tea cools faster than a hot bath, even though both involve hot water in a porcelain container. More precisely, the thermal relaxation time for heat conduction is proportional to the square of size (see Eq. 2). That is, for any given material and shape, an object half the size will cool in one fourth the time and an object one tenth the size will cool in one hundredth the time. This behavior is important in optimizing the pulse duration or the exposure duration for the selective photothermolysis of blood vessels. Blood vessels vary in size, from capillaries, which have thermal relaxation times of tens of microseconds, to venules and arterioles, which have thermal relaxation times of hundreds of microseconds, to the large venules of adult PWSs, which have thermal relaxation times of tens to hundreds of milliseconds. This means that there are vessels in a typical adult PWS with thermal relaxation times ranging over three orders of magnitude, and thus it is ludicrous to attempt to define "the" thermal relaxation time for vessels.

1: J Invest Dermatol. 1983 Jun;80 Suppl:75s-80s.

Links

Selective thermal effects with pulsed irradiation from lasers: from organ to organelle.

Parrish JA, Anderson RR, Harrist T, Paul B, Murphy GF.

Specific damage by selectively absorbed, pulsed lasers can be predicted based on physical models. Thermally mediated alterations can be confined to pigmented targets from the level of subcellular organelles (e.g., melanosomes) to large multicellular tissue structures (e.g., blood vessels) by the appropriate manipulation of wavelength and pulse duration. Highly selective damage to human cutaneous microvessels in vivo is shown to occur after 0.3-microseconds 577-nm dye laser pulses; the epidermis and dermal structures other than vessels are spared. Observations in an animal model suggest that hemorrhage or, at lower doses, selective intravascular coagulation and permanent microvascular hemostasis occur. Highly selective damage to melanized cells and to single melanosomes in situ was shown to occur after single 20-ns 351-nm pulses from a XeF excimer laser. Basal-cell- and melanocyte-specific necrosis is followed by gross hypopigmentation. In this case there is no evidence of vascular damage. The most likely modes of selective alterations include localized thermal denaturation, vaporization, and shock-wave generation. Means of predicting and controlling histologically selective radiant heating effects in skin are suggested.

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Effect of dye laser pulse duration on selective cutaneous vascular injury. [J Invest Dermatol. 1986]

Microvasculature can be selectively damaged using dye lasers: a basic theory and experimental evidence in human skin. [Lasers Surg Med. 1981]

Mechanisms of selective vascular changes caused by dye lasers. [Lasers Surg Med. 1983]

Organelle-specific injury to melanin-containing cells in human skin by pulsed laser irradiation. [Lab Invest. 1983]

Ultrastructure: effects of melanin pigment on target specificity using a pulsed dye laser (577 nm). [J Invest Dermatol. 1987]

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1: Science. 1983 Apr 29;220(4596):524-7.

Science NAAAS

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Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation.

Anderson RR, Parrish JA.

Suitably brief pulses of selectively absorbed optical radiation can cause selective damage to pigmented structures, cells, and organelles in vivo. Precise aiming is unnecessary in this unique form of radiation injury because inherent optical and thermal properties provide target selectivity. A simple, predictive model is presented. Selective damage to cutaneous microvessels and to melanosomes within melanocytes is shown after 577-nanometer (3 x 10(-7) second) and 351-nanometer (2 x 10(-8) second) pulses, respectively. Hemodynamic, histological, and ultrastructural responses are discussed.

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